#10 B
VP
3-6-01

CERTIFICATE OF MAILING
37 C.F.R. 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on the date below:

February 14, 2001
Date

Gina N. Shishima

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Jack A. Roth

Serial No.: 09/447,681

Filed: November 23, 1999

For: ADENOVIRUS p53 COMPOSITIONS (as amended)

Group Art Unit: 1632

Examiner: Crouch, D.

Atty. Dkt. No.: INRP:003--2

AMENDMENT AND RESPONSE TO OFFICE ACTION DATED AUGUST 14, 2000

Commissioner for Patents
Washington, D.C. 20231

Commissioner:

This paper is submitted in response to the Office Action dated August 14, 2000 for which the three-month date for response is November 14, 2000. A request for a three-month extension of time to respond is included herewith along with the required fee. This three-month extension will bring the due date to February 14, 2001, which is within the six-month statutory period. Should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Fulbright & Jaworski Account No.: 50-1212/10012299/01985.

Reconsideration of the application is respectfully requested.

I. AMENDMENT

In the Specification

Please amend the title of the application on page 1, line 1 by deleting "and methods."

In the Claims

Please cancel claims 66, 68-85, without prejudice or disclaimer.

Please make the following amendments:

B1 67. (Amended) An adenovirus vector comprising a wild type p53 gene under the control of a [The vector of claim 66, wherein the promoter is the] CMV promoter.

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

This application is a continuation application under 37 C.F.R. 1.53 (b) of Serial Application No. 07/960,513. In the parent application, claims 1-30 were originally filed and claims 31-65 were added by amendment. With the filing of this application, Applicants cancelled claims 1-30. Claims 66-85 were added by preliminary amendment (claims 31-65 do not exist in this case). The Office Action mailed August 14, 2000 rejected claims 66-85.

The examiner met with Applicant's representatives on January 16, 2001, which Applicant's representatives sincerely appreciate. Examiner Crouch generated the Interview Summary for that meeting. As discussed in that interview, some of the claims are being removed from consideration. Herein, claims 66 and 68-85 are cancelled and claim 67 is amended. Claim 67 has been amended herein to be in independent claim form because the claim from which it depended, claim 66, is cancelled herein. Thus, claims 67 is the subject of this response. A copy of the pending claims is provided in Appendix A.

Applicant is withdrawing the claims directed to a "method of treating a cancer cell in a patient" and a "method for treating a cell having a mutant p53 gene," both involving introducing a "wild type p53 gene" into the cell due to a restriction requirement we received in a related offspring case. In the Office Action dated June 6, 1994 in Application Serial No. 08/145,826 examiner Guzo indicated "recombinant adenoviruses" were a patentably distinct invention from "methods of restoring p53 function." In an abundance of caution, Applicant is removing the method claims arguably related to the latter invention from consideration in this case.

Applicant is removing claims directed to other promoters in an effort to focus the prosecution on those embodiments that are currently in clinical trials, particularly a phase III trial of head and neck cancer being conducted by Introgen Therapeutics and a phase II/III trial in ovarian carcinoma being conducted by Canji/Schering-Plough. It is believed that the current embodiment claimed (adenoviral CMV p53), as evidenced by the fact that two commercial entities are currently employing this embodiment in advanced clinical trials, has significant advantages associated with it and is indeed separately patentable from the genus (adenoviral p53 plus any promoter).

B. Title Is Amended

Due to the cancellation of all methods claims, Applicant is amending the title to describe more accurately the subject matter of the present application. Instead of "Adenovirus p53 Compositions and Methods," the title, as amended, reads "Adenovirus p53 Compositions."

C. Claims 66-71 Are Adequately Described under 35 U.S.C. § 112

The Action rejected claims 66-71 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to one skilled in the art that the inventors, at the time the application was filed, has possession of the claimed invention. It contends that the instant specification does not contemplate adenoviral vectors comprising a wild type p53 gene operably linked to a promoter or to a specific promoter. It further alleges that at no place in the specification is the invention clearly set forth so that the reader would realize what the applicant perceived as his invention at the time of filing. Applicant respectfully traverses this rejection.

The written description requirement is whether the "description clearly allows persons of ordinary skill in the art to recognize that he or she invented what is claimed." MPEP 2163.02 (citing *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989)). Applicant contends that it is clear that the specification describes what is claimed in rejected claims 66-71. Claim 66 recites an "adenovirus vector comprising a wild type p53 gene under the control of a promoter." The written description of this application supports this claim. First, the Specification is not limited to retroviruses. Explaining that the surprising aspect of the invention is the increase in transcription, the Specification explicitly states, "While this affect [sic] was observed using the β-actin promoter and a retroviral expression vector, the inventors believe that this phenomenon ***will be applicable to other promoter/vector constructs for application in gene therapy***." Specification at page 8, line 25 to page 9, line 4 (emphasis added). These other promoter/vector constructs are then described throughout the disclosure. For example, the Specification discloses:

> In one specific embodiment, the invention concerns vector constructs for introducing wild type p53 genes (wt-*p53*) into affected target cells

> suspected of having mutant *p53* genes. These embodiments involve the preparation of a gene expression unit wherein the wt-*p53* gene is placed under the control of the β-actin promoter, and the unit is positioned in a reverse orientation into a retroviral vector.

Specification at page 9, lines 6-12. The application expressly says, "In addition to retroviruses, it is contemplated that ***other vectors can be employed, including adenovirus***...." Specification at page 14, lines 21-23 (emphasis added). As for promoters, it further states, "While the β-actin promoter is preferred the invention is by no means limited to this promoter and one may also mention by way of example promoters derived from RSV, N2A, LN, LNSX, LNSN, SV40, LNCX or **CMV**." Specification at page 15, lines 1-4 (citations omitted) (emphasis added).

The Action contends that in the places where adenovirus or promoters claimed are disclosed, "each such disclosure is within the context of antisense RNA production." Office Action pages 3-4. Applicant denies that adenoviruses are discussed in the application only in the context of antisense embodiments. The paragraph in which the Specification discloses that other vectors such as adenovirus can be used instead of a retrovirus begins, "In broader aspects of the invention, a preferred approach will involve the preparation of retroviral vectors which incorporate nucleic acid sequences encoding the desired construct, once introduced into the cell to be treated...." Specification at page 14, lines 9-12. The use of adenovirus is discusses in the context of "broader aspects of the invention," and retroviruses and antisense constructs are but examples of aspects of the invention. Similarly, the following paragraph discussing promoters indeed recites particular embodiments of the invention, such as antisense; however, it says, "***Generally speaking***, such a promoter might include either a human cellular or viral promoter. While the β-actin promoter is preferred the invention is by no means limited to this promoter...." Specification at page 14, line 35-page 15, lines 2 (emphasis added). Furthermore, the disclosure clearly states, "While the retroviral construct aspect of the invention concerns the use of a β-actin

promoter in reverse orientation, there is no limitation on the nature of the selected gene which one desires to have expressed. Thus, the invention concerns the use of antisense-encoding constructs ***as well as 'sense' constructs that encode a desired protein.***" Specification at page 16, lines 5-10. It is clear that discussions regarding antisense constructs are applicable to embodiments concerning sense constructs, such as the p53 embodiment.

Therefore, the Specification makes clear that 1) p53 sense constructs are contemplated; 2) any discussion about antisense constructs applies to "sense" constructs such as p53; 3) constructs can be retroviral, but they may also be adenovirus constructs; 4) promoters are discussed both generally and in the context of antisense constructs, in addition to CMV being specifically mentioned; and finally, 5) since an adenovirus can be used instead of retrovirus and since constructs are not limited to antisense constructs, applying equally to sense constructs, there is adequate written description for an "adenovirus vector comprising a wild type p53 gene under the control of a promoter," as well as for vectors with a CMV promoter.

Applicant also submits as evidence the Declaration of Louis Zumstein, Ph.D under 37 C.F.R. § 1.132, which supports the contention that the claims of the invention are adequately described by the Specification.

Since the Specification indicates to a skilled artisan that the inventor was in possession of the claimed invention at the time the application was filed, Applicant respectfully requests this rejection be withdrawn.

D. Claims 67-71 Are Definite

Claims 67-71 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite with respect to "the XXX promoter." Claims 67 has been amended to recite a promoter with the indefinite article "a" instead of the definite article "the."

E. Priority Date Is Not Accurate

The Action contends that the application has been given a priority date of October 29, 1993, the filing date of 08/145,826 ('826 application). The present application claims priority to 07/960,513 ('513 application), filed October 13, 1992. Applicant is confused because the '826 application has never been mentioned as a priority application in this case and because the Action levies a written description rejection based on the '513 application, not the '826 application. Applicant once again asserts the priority claim of the present application to the '513 application.

F. Claims 66-71 Are Nonobvious under 35 U.S.C. § 103 (a)

The Action rejected claims 66-71 under 35 U.S.C. § 103 (a) as being unpatentable over Chen *et al.* (Chen) in view of Willinson *et al.* (Wilkinson), Colicos *et al.* (Colicos), Rajan *et al.* (Rajan), and Hitt *et al.* (Hitt). It alleges that the Chen references teaches that wild-type p53 is expressed in transduced cells and that these cells fail to form tumors in nude mice. The Action admits that this reference does not teach an adenoviral vector comprising a wild-type p53 gene under the control of a promoter, but instead, relies upon Wilkinson as allegedly teaching an adenovirus expression system utilizing a CMV promoter to regulate expression of *lacZ*. The Action also contends that Colicos teaches an adenovirus vector containing the RSV promoter,

that Rajan teaches an adenoviral vector containing an SV40 promoter, and that Hitt teaches an adenovirus vector with a human β actin promoter. The Action further argues that the motivation to make the claimed vectors is provided by the Chen reference's statement that expression of p53 in cells lacking functional p53 reverts the cells' transformed phenotype and suggests possible clinical use of p53 gene replacement. Applicant respectfully traverses this rejection.

The Federal Circuit held in *In re Mills*, 916 F.2d 680, 682 (Fed. Cir. 1990), that the mere fact that combination or modification of a reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. *Id.*; *see also* MPEP § 2143.01, page 2100-91. Alternatively, Federal Circuit caselaw requires motivation ***to combine references***. "To combine references (A) and (B) properly to reach the conclusion that the subject matter of a patent would have been obvious, case law requires that there must be some teaching, suggestion, or inference in either reference (A) or (B), or both, or knowledge generally available to one of ordinary skill in the relevant art that would lead one skilled in the art to combine the relevant teachings of references (A) and (B)." *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 U.S.P.Q. 657 (Fed. Cir. 1985). The Action has not satisfied either. It provides neither the basis for combining the Chen reference with the Wilkinson reference or the basis for combining the adenovirus vector of Wilkinson with the wt p53 gene of Chen. The Action states, "Motivation is provided by Chen et al stating that expression of p53 in cells [sic] Saos cells which lack functional p53 reverts the transformed phenotype, and that such suggests possible clinical use of p53 gene replacement." This basis is simply not sufficient for a *prima facie* case of obviousness.

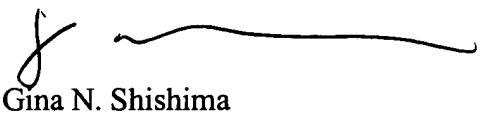
Furthermore, "[i]t is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any on reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 U.S.P.Q. 416 (Fed. Cir. 1986). The Chen reference purportedly discloses a retroviral vector comprising a wild-type p53 gene sequence. There is no suggestion in any of the cited references that one should replace the retroviral vector of Chen with the adenoviral vector of Wilkinson for the *p53* construct, any more than there is the suggestion to make the retroviral vector of Chen with the ***lacZ* gene** of Wilkinson.

With respect to the rejected dependent claims, there is similarly no suggestion in any of the cited references to choose particular aspects of those references and combine those aspects with one another or to simply combine those references. Once again, Chen allegedly teaches a retrovirus vector with a wild-type *p53* gene under the control of an LTR promoter; Wilkinson allegedly teaches an adenovirus vector with a *lacZ* gene under the control of a CMV promoter. The references of Colicos, Rajan, and Hitt are cited respectively for the use of an adenoviral vector comprising an RSV promoter, the use of an adenovirus with an SV40 promoter, and the use of an adenovirus with a β-actin promoter. In each case the promoter drives the expression of a gene that is not a p53 gene and that is different from the other cited references. The Action merely points to references that disclose elements of the claimed invention and asserts it would have been obvious to the ordinary artisan at the time of the invention to use an adenoviral vector comprising a human wild-type *p53* gene operably linked to a specific promoter. Such an artisan would have to pick out *p53* as the gene to be expressed in an adenovirus vector and under the control of specific promoters. Applicant contends that the absence of a suggestion or motivation

to combine renders any *prima facie* case of obviousness based on these references to be fatally flawed. Accordingly, Applicant contend that the vector claims are patentable over the cited references, and respectfully requests the withdrawal of this rejection for claim 67.

The Examiner is invited to contact the undersigned attorney at (512) 536-3081 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



Gina N. Shishima
Reg. No. 45,104
Attorney for Applicant

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3081

Date: February 14, 2001